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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,769	04/04/2001	Milan S. Blake	NV1932	3657

7590 07/09/2004

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/825,769	BLAKE ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 May 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: NONE.

   Claim(s) objected to: NONE.

   Claim(s) rejected: 13-17.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: See Advisory Attachment.

Continuation of 3. Applicant's reply has overcome the following rejection(s): rejection of claim 17 under 35 U.S.C. 112, second paragraph, page 6, paragraph 7 and rejection of claims 11-17 under 35.U.S.C. 112, second paragraph, page 6, paragraph 8.

Advisory Action Attachment

1. Applicants amendment filed May 6, 2004 is acknowledged. Claim 17 has been amended. Claims 1-12 have been cancelled.

Objection/Rejection Withdrawn

2. In view of Applicant's amendment the objections and rejections are withdrawn:

a) objection of the drawings, new formal drawings (figure 7) filed September 30, 2004.

b) rejection of claim 17 under 35 U.S.C. 112, second paragraph, page 6, paragraph 7.

c) rejection of claims 11-17, under 35 U.S.C. 112, second paragraph page 6, paragraph 8.

Rejections Maintained

3. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims 13-17 for the reasons set forth on pages 3-5, paragraph 6 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which lacks written description in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

The claims are drawn to a method for producing PT comprising a *B. pertussis* cysteine desulfinase knockout mutant in a *B. pertussis* culture medium and isolating the PT from the culture medium and a method of enhanced production of PT comprising cultivating B. *pertussis* cysteine desulfinase knockout mutant.

The claims broadly encompass a genus of cysteine desulfinase genes. There is substantial variability among the species of cysteine desulfinase genes encompassed within the scope of the claims. The specification does not place any structure limitations on the cysteine desulfinase gene. The scope of the claims include numerous structural variants and the genus is highly variant because a significant

number of structural difference between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the gene class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. Since there is no structure in the claim to define the cysteine desulfinase gene, the claimed genus includes cysteine desulfinase genes produced by other microorganisms. For Example, Mihara et al, *(The Journal of Biological Chemistry, Vol. 272, No. 36, p. 22417-22424)* teach that *Escherichia coli* appears to contain three nifS-like genes which encode NIFS-like protein (page 22417). Mihara et al teach that the NIFS-like proteins encoded by the nifS gene of *E. coli* has cysteine desulfinase activities. Mihara et al teach that nifS and NIFS-like proteins are found in a number of microorganisms (see Table III). Since the claimed genus encompasses genes of other microorganisms and genes yet to be discovered, the mere recitation of a "cysteine desulfinase knockout mutant" does not provide an adequate written description of the claimed genus since no structure accompanies the function of cysteine desulfinase activity. One skilled in the art would not recognize from the claimed disclosure that the applicant was in possession of the genus of nucleic acid sequences that are required to use the claimed method of producing PT comprising a *B. pertussis* cysteine desulfinase knockout mutant in a *B. pertussis* culture medium and isolating the PT from the culture medium. The recitation of "cysteine desulfinase knockout mutant" does not convey a common structure. As such, generic nucleic acid sequences that are unrelated via structure are highly variant and not conveyed by way of the written description in the specification at the time of filing. Therefore, the specification lacks written description for the highly variant genus of nucleic acid sequences that have cysteine desulfinase activity and one of skill in the would not recognize that Applicants had possession of the genus of the claimed genes for use in the method as instantly claimed method.

Applicant refers the Examiner to the Written Description Guidelines (66 Fed. Reg. 1099), 2001, republished at MPEP 2163. Applicant urges that according to the guidelines, possession of a claimed invention can be shown by disclosure of structural characteristics, functional characteristics that correlate with structure or combinations thereof. Applicant urges that the Examiner has not satisfied these guidelines in making the rejection. Applicant urges that they were in possession of the claimed subject matter. Applicant urges that the DNA sequences (paragraphs 40-43) teach the skilled person that any nucleotide sequence can be inserted into the cysteine desulfinase gene

in order to interrupt the gene and in some embodiments the sequence is a maker gene. Applicant urges that such sequences are readily available and apparent to the skilled person and therefore applicants were in possession of such DNA sequences.

Applicant's arguments filed May 6, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show that the specification is enabled for the full scope of the claims and therefore does not meet the written description requirement as set forth in 35 U.S.C. 112, first paragraph.

The Examiner disagrees with Applicant in there assertion the Examiner has not met the burden under the Written Description Requirement. MPEP 2163.04 states:

> The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. Wertheim, 541 F.2d at 263, 191 USPQ at 97.
>
> I. STATEMENT OF REJECTION REQUIREMENT
>
> In rejecting a claim, the examiner must set forth express findings of fact which support the lack of written description conclusion (see MPEP § 2163 for examination guidelines pertaining to the written description requirement). These findings should:
>
> (A) Identify the claim limitation at issue; and (B) Establish a prima facie case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description. A simple statement such as "Applicant has not pointed out where the new (or amended) claim is supported, nor does there appear to be a written description of the claim limitation ____' in the application as filed." may be sufficient where the claim is a new or amended claim, the support for the limitation is not apparent, and applicant has not pointed out where the limitation is supported. When appropriate, suggest amendments to the claims which can be supported by the application's written description, being mindful of the prohibition against the addition of new matter in the claims or description. See Rasmussen, 650 F.2d at 1214, 211 USPQ at 326.

In the instant case, the specification broadly describes a genus of cysteine desulfinase genes. There is substantial variability among the species of cysteine

desulfinase genes encompassed within the scope of the claims. The specification does not place any structure limitations on the cysteine desulfinase gene. The scope of the claims include numerous structural variants and the genus is highly variant because a significant number of structural difference between genus members is permitted. While the use of probes, hybridization tools and mutagenesis techniques are known in the art, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the nucleic acid's sequence where nucleic acids modifications can be made with a reasonable expectation of success in obtaining the desired activity are limited in any nucleic acid molecule and the result of such modifications is unpredictable based on the instant disclosure. The claims also encompass the use of DNA sequences integrated into a *Bordetella pertussis* cysteine desulfinase gene. The specification does not place any structure limitations on the cysteine desulfinase gene nor does the specification place any structure limitations on the DNA sequences integrated into a *Bordetella pertussis* cysteine desulfinase gene. It should be noted that a review of the specification indicates that the elements which are not particularly described, including regulatory element and untranslated regions are essential to the function of the claimed invention. Applicant has recited in claim 13 that the function (i.e. lacking cysteine desulfinase activity) is essential to the claimed method. It is well known in the art that the structure of genes with naturally occurring regulatory elements and untranslated regions is empirically determined. Example 6 of the Written Description Guidelines teach that the structural elements of a "gene" mediating the expression of a particular gene may differ depending on where the gene

is expressed. Therefore, the structure of these elements which Applicant considers as being an essential to the function of the claim are not conventional in the art. There is no correlation between the function (i.e. lacking cysteine desulfinase activity) and the structure of the non-described regulatory elements and untranslated regions of the gene. Therefore, the specification lacks written description for the highly variant genus of nucleic acid sequences that have cysteine desulfinase activity and one of skill in the would not recognize that Applicants had possession of the genus of the claimed genes for use in the method as instantly claimed method.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

5. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
July 1, 2004

MARK NAVARRO
PRIMARY EXAMINER